THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES
AUGUST, 1922

## ORIGINAL ARTICLES.

# THE ACTION OF DIGITALIS IN CASE OF AURICULAR FIBRILLATION AND FLUTTER.*

### THIRD LECTURE

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The original observations upon which this lecture is largely based have been carried out by my collaborators and myself during the past twelve months to determine if the reaction of auricular fibrillation and auricular flutter to therapeutic doses of digitalis may be explained by the theory that these two disorders of heart rhythm are essentially due to circus movement.† First we will consider the action of digitalis upon the rate of the ventricle, and later we will consider the main problem of its action on the auricle. As will appear, knowledge of the first is relevant when we explore the second problem.

**The Nature of Digitalis Block.** The question as to how digitalis produces heart-block, the universally recognized cause of ventricular slowing in cases of auricular fibrillation, is one upon which a conflict of opinion exists. The evidence is not of so simple a character as it was once thought to be. The discussion is rendered of more consequence because precisely similar problems arise in the case of ventricular slowings other than those due to digitalis and in other forms of slow ventricular action. The argument turns, as we shall presently see, mainly upon the reaction of the ventricle to atropine.

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* Based on observations carried out on behalf of the British Medical Research Council. The Nathan Lewis Hatfield Lecture, delivered before the College of Physicians of Philadelphia, May 5, 1922.

† Especially associated with me in the most recent observations have been Dr. A. M. Wedd, of Pittsburgh, and Dr. C. C. Iliescu, of Bucharest; we have also received much assistance from Dr. A. N. Drury, who has for some years worked actively upon closely allied problems.

We start with the simple and uncontested fact that digitalis produces ventricular slowing in cases of auricular fibrillation; and we conclude from evidence in our possession that this retardation is due to block at the *A-V* junction.[8] Experiment teaches us that *A-V* block may be produced by digitalis in one of two ways, by increasing the tone of the vagus (an indirect effect exerted upon the junctional tissues) or by a direct action on the junctional muscle.[3, 11, 16] The action, whether direct or indirect is exerted, according with, the indications of recent experiment, upon that portion of the junctional tissues termed the *A-V* node.[11] The direct and indirect action each has the same end-effect; each produces a condition at the *A-V* node rendering it less capable of conveying impulses. The immediate effects upon the tissue are not quite the same; in the case of the nerve effect, we have to deal apparently with a reduced rate of recovery of the tissue; in the case of the direct action we have to deal apparently with a prolongation of systole, whereby the time allowed for subsequent recovery is reduced. Be that as it may the end-effects are both declared as lesser or greater degrees of block. Block at the *A-V* junction is the only known means by which digitalis can influence the rate at which the ventricle will respond to an auricle in a constant and unaltered state of fibrillation. Is this block produced by a direct action or by an indirect action through the vagus in clinical fibrillation? The problem would appear easy to solve. Digitalis slowing is produced in a case of fibrillation and the patient is then atropinized. The atropine paralyzes the vagus and the ventricular rate returns to about its former level. What more natural than to conclude that digitalis exerts its action through the vagus. That is the conclusion to which Mackenzie came,[12] when he first used atropine for this purpose. But, as Cushny[4] has very properly pointed out, the problem does not end here. Cushny's argument is one of some intricacy and has not been understood widely and clearly. It may be illustrated diagrammatically (Fig. 1). Let us suppose that the line *cc* represents the level at which the ventricle beats in response to a fibrillating auricle when the patient is uninfluenced by drugs; and let us further suppose that this rate is reduced from *c* to *e* under the influence of digitalis given in therapeutic doses. Atropine is now given, and the rate returns, let us say, from *e* to *c*. The fall which digitalis produced is completely wiped out by the action of the atropine. Yet we are not justified in concluding that the digitalis fall of rate from *c* to *e* is vagal in origin. As Cushny has shown, if an initial dose of atropine is given in the predigitalis stage, the rate is lifted temporarily to *a*. In other words, the original level *c* was maintained at a comparatively low point by normal reflex vagal tone; and when this level is further reduced (to *e*) by digitalis, the subsequent rise produced by atropine may be attributed to one of two effects: (1) To the abolition of the original reflex vagal tone prevailing at level *c* and still maintained after digitalization, or (2) to the abolition of a digitalis vagal tone.

To obtain *proof* that the fall on digitalis is due entirely to an increase of preëxisting vagal tone, one view which has been held of the action of digitalis, it would be necessary to show that atropine can raise the rate of the digitalized heart from level *e* to level *a;* for atropine, given in a sufficient dose to completely paralyze the vagus, should abolish, not only the original reflex vagal tone, but also that portion of the final vagal tone which has been superadded by the digitalis. The view may be held justifiably that the rise from *e* to *c* under atropine, is due, as was the original rise from *c* to *a*, to the abolition of normal reflex vagal tone and that the fall from *c* to *e* under digitalis was in reality the effect of a direct action which has been uninfluenced by the second dose of atropine. The level (*c*) at which the ventricular rate stands after digitalis and atropine is far below the level (*a*) at which it stands under atropine alone, and this should not be the case, providing that the digitalis fall is purely vagal, and if a dose adequate to abolish all vagal action is given on each occasion. Thus, it is evident that the final rise under atropine from *e* to *c* cannot be used as proof that the action of digitalis is vagal.

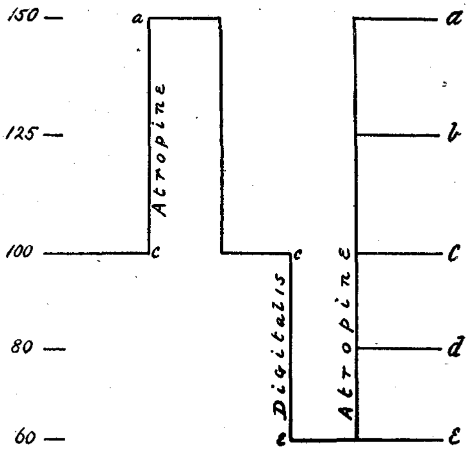

Fig. 1.—A diagram of the reaction of the ventricle, in auricular fibrillation, to digitalis and atropine. The diagram illustrates the text description.

On the other hand it cannot be used as proof that the action is purely a direct one, the second view of digitalis action which has been held. *Proof* of a purely direct action would be obtained only if the second and adequate dose of atropine failed to produce a rise, namely, if the level remained stationary at *e*. It may be argued that since the rise from *e* to *c* is no greater than the rise from *c* to *a*, this relation constitutes evidence that both these rises are due simply to the abolition of the original reflex vagal tone, and that digitalis vagal tone plays no part in the fall *c* to *e*. This argument is only valid if a certain measure of vagal tone produces equal falls of ventricular rate from different initial levels and if we can be sure that when the ventricle slows under digitalis *the original measure of reflex vagal tone is maintained;* but the first assumption is scarcely justified, since a halving of ventricular rate is produced more easily when the rate of the ventricle is initially high than when it is low, and a halving of rate at a high level means a much larger fall in the number of beats per minute than does halving at a lower rate. In respect of the second assumption it may be argued that, when the heart slows under digitalis, the natural reflex vagal tone would tend to pass into abeyance and might vanish entirely.

We are left therefore in this position. Proof of uncomplicated vagal action requires a lift of rate from *e* to *a*. Proof of uncomplicated direct action requires maintenance of the level at *e*.

Now, neither one nor the other form of curve characterizes the actual reaction. The rate does rise when an adequate dose of atropine is given, but it rises to very different levels in different patients. In the series described by Mackenzie and by Cushny, the rise was generally either to a level intermediate between *e* and *c* or actually, as in Mackenzie's case, to *c*. It will be clear that the less the rise, the more is a direct action evidenced; the greater the rise, the more is vagal action evidenced; but that, so long as there is a rise, but a rise which fails to reach level *a*, *proof* of an uncomplicated action, direct or indirect, is not forthcoming.

**The Dose of Atropine.** The assumption that the dose of atropine given is adequate completely to paralyze the vagus is one of such consequence to the argument that it needs to be explored in some detail.

Actually the dose required to paralyze the human vagus has not been ascertained either for normal subjects or for cases of fibrillation, digitalized or undigitalized. The general assumption appears to be that one-fiftieth of a grain of the sulphate given hypodermically is sufficient.

This assumption appears to be based in part upon the belief that atropine has an "all or nothing" action; that if the ventricle is released at all, it is fully released. The last belief is not well founded. If atropine is injected intravenously repeatedly and in minute doses into dogs, it is not difficult to show that the drug first abolishes the effects of weak vagal stimulation, and that further doses are required before the effect of strong vagal stimulation disappears. In dogs weighing 10 kgs. a dose of 0.2 to 0.4 mg. of atropine will abolish the effects of weak stimulation; in the same dogs doses of 0.4 to 1.0 mg. are required to abolish the effects of strong stimulation. The dose required to produce complete paralysis is approximately 0.05 to 0.1 mg. of atropine per kilo body weight. Calculated on the same bases for a human subject of 75 kilo weight, the dose required would be 3.7 to 7.5 mg. (or approximately one-seventeenth to one-ninth of a grain). From this calculation it might be anticipated that one-fiftieth of a grain given to the human subject would on direct tests prove to be inadequate. At the same time it should be noted that while in dogs doses of from 0.2 to 0.4 mg. will not abolish all reaction, yet they very notably reduce the reaction to strong stimulation of the nerve. Thus, it is to be inferred that since one-fiftieth of a grain given to a patient is sufficient to produce a conspicuous rise of ventricular rate, a large subsequent rise of rate on completely saturating the vagus with atropine is not to be expected.

**Clinical Observations.** With few exceptions the dose given in published cases has been one-fiftieth of a grain of atropine sulphate administered hypodermically. In one of Cushny's cases one-fiftieth of a grain was administered on one occasion and one-twenty-fifth of a grain on a second occasion, the ventricular rate rising to approximately the same level on the two occasions.[4] It has been felt that this single observation, from which it is argued that one-fiftieth of a grain is an adequate dose, constitutes insufficient evidence; in a preliminary series of observations upon three cases of auricular fibrillation, we gave separately and at suitable intervals doses of one-twentieth and one-tenth of a grain with a view to comparing the resultant ventricular curves. In two cases no difference was apparent; in the third case the rise with the one-tenth of a grain was appreciably the higher. In a second series of observations upon similar cases we have given one-fiftieth of a grain of atropine hypodermically, and have followed this by a further and intravenous injection at the height of the reaction to the first dose. The results are variable. In some few patients one-fiftieth of a grain given hypodermically appears to be adequate. More frequently, however, the rate rises further on the second dose (Figs. 2 and 3). The second rise amounts to as much as 10, 15 or 20 beats per minute. Through and through this added rise seems to be greater in patients who have previously been brought under the influence of digitalis. That is to be expected if we take the view that a dose adequate to cut out normal reflex vagal tone is not necessarily adequate to abolish this tone and also that which we might suppose added during the period of digitalis slowing.

Thus it would appear that the doses used to test the measure of vagal tone in both the digitalized and undigitalized case have not always been adequate. The curves published by Mackenzie

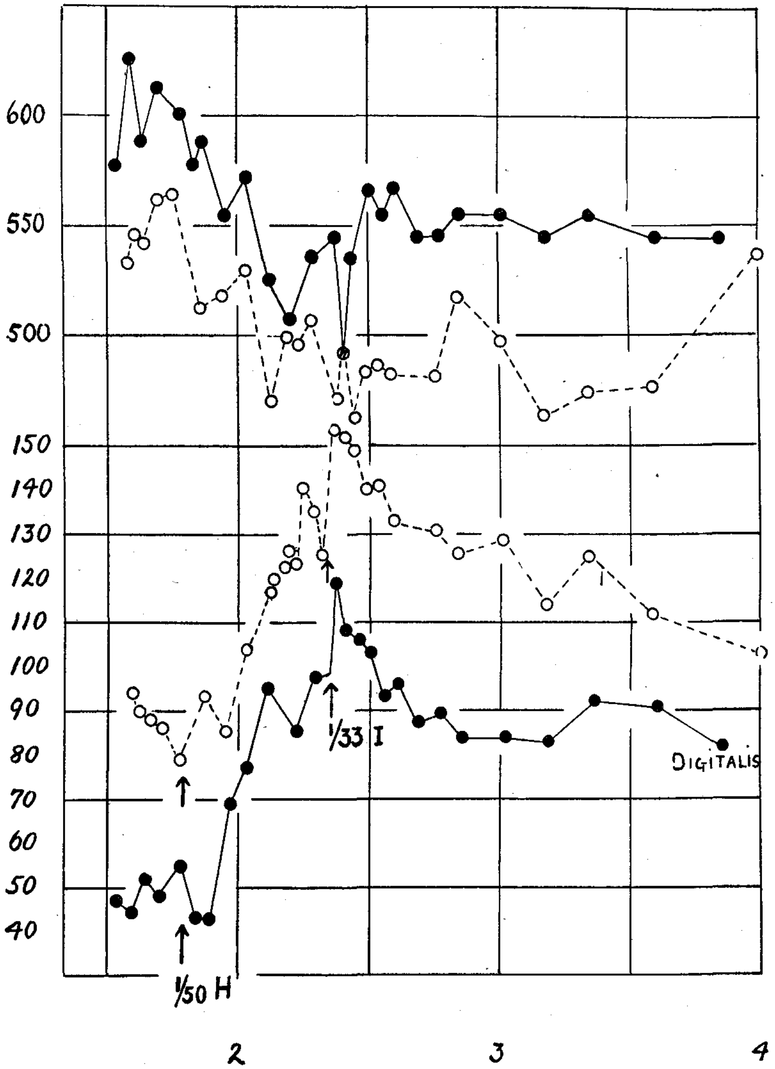

FIG. 2.—A chart of the auricular (upper curves) and ventricular rates (lower curves) in a case of fibrillation of the auricles. The curves were constructed from the patient while digitalis free (plain circles) and while under digitalis (black circles) 7½ drams of tincture had been taken in eight days. In both circumstances a hypodermic dose of $\frac{1}{50}$ of a grain of atropine was followed by an intravenous dose of $\frac{1}{33}$ of a grain.

and Cushny to illustrate the effects of abolishing vagal tone in digitalized patients cannot be regarded as wholly representative.

When fuller doses, single doses of one-tenth or of one-twentieth of a grain, or two doses bringing the total to one-twentieth of a grain, are administered, the rise is almost always above the level of the predigitalized rate (level *c*); often it is considerably above this rate and exceptionally it may approach very closely to the rate obtained by the similar administration of atropine in the predigitalis stage (level *a*). Of the two procedures the former appears to be the more effective (Fig. 3), and presumably this is so, because when a hypodermic dose is given the reaction is not usually at its height for

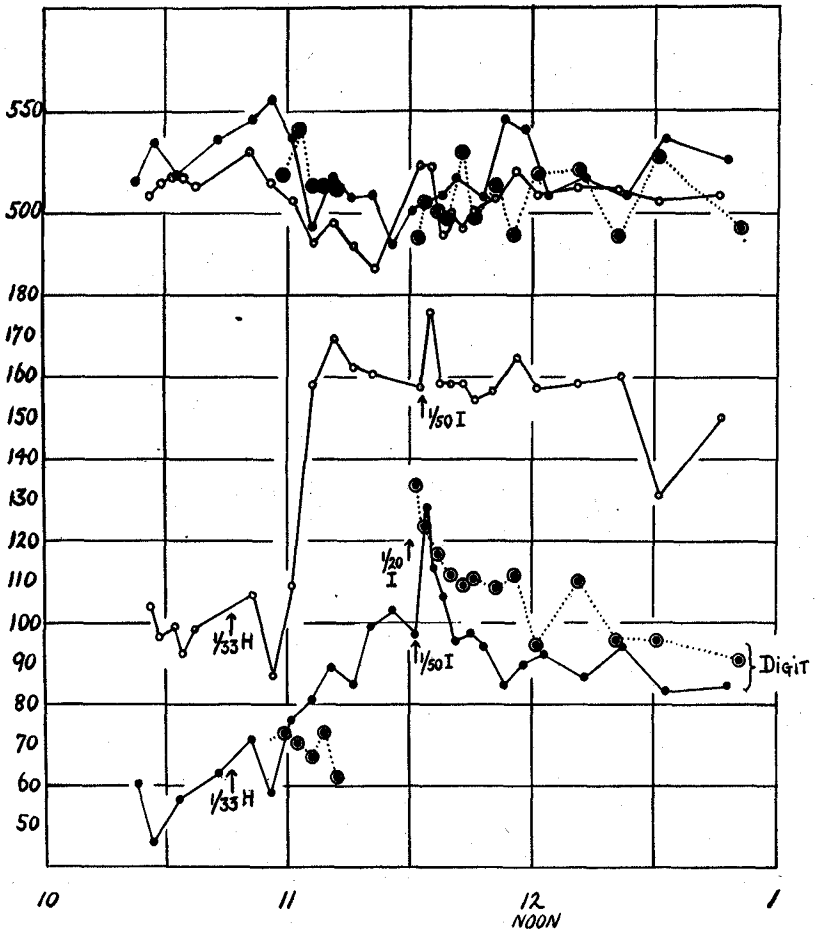

Fig. 3.—A similar chart from a second patient, to which has been added the curve produced by a single intravenous dose of $\frac{1}{20}$ of a grain of atropine (double-circles) while the patient was still under digitalis. The hypodermic injections in the case of the first curves were $\frac{1}{33}$ of a grain and the intravenous doses were $\frac{1}{50}$ of a grain. 9½ drams of tincture of digitalis had been taken in eleven days.

twenty minutes, while if a similar intravenous dose is given, recovery usually begins before this time has elapsed. It is to be concluded therefore that the full effect of one-fiftieth of a grain is not always shown when the drug is given hypodermically. In one patient (Fig. 4) the original rate was 101, and atropine (one-twentieth of a grain) drove the rate to 232. The patient was now given full therapeutic doses of digitalis and the rate fell to 70; a dose of one-twentieth of a grain now increased the rate to 205. The first atropine rise was of 131 beats, the second of 135 beats. It is to be observed that the full rate of 232 was not attained at the second injection, consequently it cannot be concluded finally that the digitalis slowing in this case was of purely vagal origin; but it

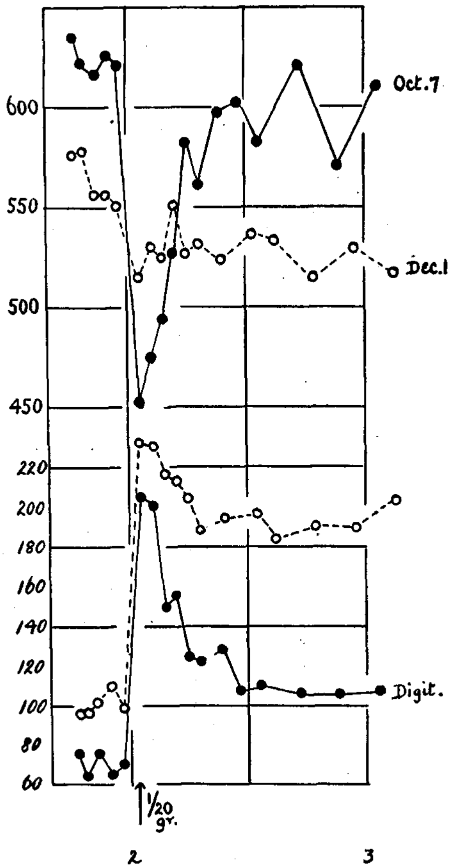

FIG. 4.—The effects of injecting $\frac{1}{20}$ of a grain of atropine intravenously in a case of auricular fibrillation, before (plain circles) and after (black circles) bringing the heart under the influence of digitalis (9 drams of tincture in twelve days).

can be concluded with some approach to finality that in this case the digitalis slowing was in large part vagal in origin, for the second dose of atropine almost abolished, not only the fall on digitalis but also the preëxisting reflex tone. The differences before and after the administration of digitalis was one of 31 beats per minute; the difference in the maximal rates attained under atropine was 27 beats. These two differences cannot reasonably be regarded as equivalent; the first, occurring while rates of 200 or over prevailed, is a minor difference as compared with that obtained at rates of 100 and under.

In view of such observations it seems reasonable to conclude that in some cases of auricular fibrillation, digitalis does exert an influence through the vagus and that in greater or lesser measure this increase of vagal tone is responsible for the ventricular slowing. It still cannot be concluded that in any patient, the fall of rate is wholly vagal; neither can it be said that an increased vagal tone is present in all these patients during digitalis slowing, observations are still insufficient to determine the percentage of cases so influenced or the precise degree in which the two factors are called into play. To embrace all cases of auricular fibrillation, our conclusion must remain tentative. We may sum up by stating that in the light of experimental and clinical observations it seems clear that digitalis exerts a twofold action, a direct and an indirect one, both of which decrease the facility with which impulses are conveyed across the *A-V* junction; both of which therefore reduce the rate of the responding ventricle. A similar conclusion has been reached by Robinson and Wilson[14] arguing from experimental data, and by Cohn[1] who argues mainly from clinical data. The proportion in which these two actions are exerted is probably variable in cases of fibrillation of the auricle; in some cases the vagal action appears to be the more conspicuous factor; in others, very probably, the direct action is predominant.

The importance of these conclusions will become more evident when we study the action of digitalis upon the auricle in auricular fibrillation.

**Action upon the Fibrillating Auricle.** Generally speaking it has been assumed that in cases of auricular fibrillation, exposed to the influence of digitalis, the auricular action remains constant, and that the whole effect upon the ventricular rate is localized in the junctional tissues. This is not strictly true; for the auricle is also affected. The action is not an entirely constant one, but in the majority of patients the oscillations recorded from the auricle are decidedly increased in rate (Figs. 2, 3 and 4). This change is studied in curves taken by means of direct leads from the chest wall, in which curves the electrical events in the auricle are represented in a comparatively pure form. Of 11 cases investigated, the oscillations showed no appreciable change of rate in 3 cases;

in 1 case there was a fall of rate; while in the remaining 7 cases there was a decided or conspicuous rise of rate; in 2 cases the rise amounting to 60 or 70 beats per minute.

To what is this usual rise of rate due? To answer this question we must clearly understand the nature of auricular fibrillation. This mechanism, according to the theory we support, is the result of a continuously circulating wave in the auricle. The circus movement controls the rate of the auricular oscillations, each oscillation corresponding to a complete auricular circuit. The time in which these circuits are completed actually depends upon two factors, (*a*) the length of the path followed and (*b*) the rate at which the wave travels. But the length of path is itself controlled by the length of the refractory period at any one point in the muscle and by the rate of conduction. Consequently we may say that the time in which a circuit is completed is controlled by two factors, namely, (1) the length of the refractory period and (2) the rate of conduction. As the rate of the oscillations per minute is due to the duration of individual circuits, it will be evident that the rate of oscillation is controlled by the same two factors.

A lengthening of the refractory period, by lengthening the path, will tend to increase the duration of each circuit and will slow the oscillations. Conversely, a shortening of the refractory period will tend to accelerate the oscillations.

Slowing of conduction will lengthen the circulation time and decrease the rate of oscillations; quickening of conduction, will increase the rate of the oscillations.

Now digitalis has two effects on the heart muscle. Insofar as it acts by increasing vagal tone it will reduce the length of the refractory period and it will tend to increase the rate of conduction. Thus, a vagal action of digitalis theoretically will reduce the time of circulation, will increase the rate of the oscillations. In experiment, vagal stimulation is well known to exert this influence upon the oscillations of a fibrillating auricle.[10] [15]

On the other hand, digitalis, acting directly on the muscle, increases the length of the refractory period and retards conduction.[11] Theoretically, this direct action will increase the duration of the circulation time and slow down the oscillations. In anesthetized dogs, when a drug of the digitalis group is given, the vagal part of the drug's action is usually little in evidence, the chief action is a direct action. In such, the injection of the drug tends, as is expected, to slow the oscillations of the auricle which has been forced to fibrillate.

It is to be remarked that, when we are dealing with the rate of ventricular beating, both the direct and indirect actions of digitalis are exerted in the same direction, *i. e.*, toward ventricular slowing. But in the case of the fibrillating auricle, the direct and indirect actions are opposed to each other, and may in large part neutralize each other.

Because in actual observation we find it to be the rule that the auricular oscillations are increased in rate, it seems impossible to avoid concluding that the predominant action of the drug is through the vagus, so far at least as the auricle is concerned. The nature of the *A-V* block resulting from digitalis has been discussed and the observations of Cushny have been revised, mainly because, if his conclusion that this action is purely a direct one in cases of fibrillation of the auricle is correct, it would stand in conflict with what appears to be the inevitable conclusion in the case of the auricle itself. The revision of his work on the ventricle has led us to a conclusion which is compatible with the observations upon the auricle. Both the direct and indirect factors come into play. Just as in the case of the ventricle, so in the case of the auricle, the proportion between the direct and indirect actions is variable. In the case of the auricle, in virtue of the fact that the two effects of digitalis are manifested in opposite directions, it is an easier matter to ascertain their proportion than is the case with the ventricle, where the two effects are manifested in one and the same direction. An increase in the rate of the auricular oscillations, which appears to be the rule, signifies predominant vagal action; a decrease, which is sometimes seen, indicates a predominant direct action; unaltered rate indicates a balance between the two influences.

**Conversion of Flutter into Fibrillation by Digitalis.** In 1911 Mackenzie[12] reported two cases of paroxysmal tachycardia, in both of which digitalis appeared to exercise a beneficial effect. The tachycardia, in each case of obscure form, gave place to fibrillation of the auricles under digitalis, and subsequently a normal rhythm was resumed. In the first of these cases, historically the more important of the two, I took electrocardiograms from the patient during his period of tachycardia. These curves I was at the time unable correctly to interpret, but they were published in Mackenzie's paper.

In the following year I was able to report upon a similar case in which a long-continued tachycardia was converted by the action of digitalis into fibrillation of the auricles with a subsequent resumption of the normal rhythm;[7] and was able to identify the original tachycardia of this case with those previously reported by Hertz and Goodhart[5] and Jolly and Ritchie,[6] and termed by the latter writers "auricular flutter." The observations upon this case further enabled me in the same article to place a final and correct interpretation upon the case reported by Mackenzie; it became evident in the light of the new case that Mackenzie's case had also been one of flutter. A series of cases in which a similar reaction to digitalis was observed was reported at a later date[9] and was soon followed by confirmatory observations by Ritchie and others.[13] The curious reaction, by which flutter of the auricle is converted to fibrillation, soon became well known and is now widely recognized. So far, however, it has not been explained.

The chief differences between clinical flutter and fibrillation, which have as yet been established, are that in the last condition the oscillations are more rapid and that they have not the regular incidence of those seen in flutter. According to our views the first difference may be interpreted to mean that the circuit movement is completed more rapidly, the second difference is due to irregular conduction in the case of fibrillation. What is the underlying cause of these differences? On this question it is still impossible to speak with certainty. The rapidity with which the circus movement is completed in fibrillation may be due either to more rapid conduction or to a shorter path.

It is very difficult to assume the first for several reasons. In general, the more rapidly an auricle beats, the slower will its tissue conduct, so that actually we should expect fibrillation to be associated with slower and not with faster conduction. If we were dealing with fibrillation in one patient and flutter in another, this argument would lose much of its force; but we have to face the fact that both flutter and fibrillation may occur as stable mechanisms in one and the same patient, under surrounding conditions which appear to be identical. Thus flutter, which has long been stable, may be converted into fibrillation by digitalis, and this may and often does continue as a stable mechanism, long after the action of digitalis has passed away. The reverse change may sometimes be accomplished by the use of quinidine. It is difficult to believe that the rate of conduction (at a given rate of beating) is permanently altered as an after-effect of administering one or other of the drugs. A second argument against faster conduction in fibrillation, is the irregularity of conduction, such irregularity being known to result when the conduction power is pressed to its utmost and is at its slowest. We are, therefore, probably correct in assuming that conduction is slower in the fibrillating auricle than in the fluttering auricle; but this difference fails to explain why the rate of oscillation is higher in fibrillation than in flutter; we turn to the alternative.

Does the difference consist in the length of path followed, the path being shorter in fibrillation than in flutter? Here again we have no direct and conclusive evidence, but there is some which is very suggestive. If we exclude faster conduction in fibrillation, then a shorter path may be due to shortening of the refractory period, it being assumed that in fibrillation the crest of the circulating wave always follows closely on the wake of retreat; in these circumstances the actual length of path would be controlled by the length of the refractory period, the wave at once entering muscle in which recovery is expedited. This view, that the refractory period in fibrillation is less than in flutter, has been put forward already by Rothberger and Winterberg, for it is consistent with the known relation between refractory period and rate of beating, the former becoming of shorter duration as the rate rises.

The path in fibrillation may be shorter than in flutter for another reason. In the first condition we conclude that the gap between the crest of the wave and its wake is a very short one; and we come to this conclusion because conduction is irregular in fibrillation and the path varying. In flutter, on the other hand, the rate of conduction is constant and the path unvarying; this difference in the two mechanisms is consistent with the view that while the gap is short in fibrillation it is longer in flutter; the wave would then enter tissue in which an appreciable time for recovery has elapsed, whereby recovery of the tissue functions is carried further and to a more uniform point. Now a longer gap, other conditions being equal, would mean a longer path and a slower circulation time. Thus the essential distinction between fibrillation and flutter may consist in the length of the gap. This assumption would certainly seem to explain the observed differences between the two disorders.

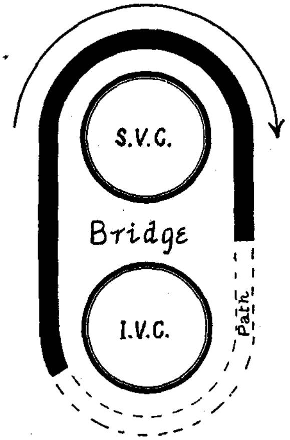

FIG. 5.—A diagram of circus movement around the superior and inferior vena cava, to illustrate how, when an appreciable gap exists, the wave may be unable to pursue a shorter course between the cavæ, unless the refractory period shortens. The diagram and its explanation suggest why the passage of flutter to fibrillation, or the reverse passage, should be an abrupt one.

If we accept this idea as a working hypothesis, it follows that the path travelled in flutter is compulsory to this extent, that the head of the wave is unable to make a short cut and thus to approach more closely to its own wake. To explain this conception in more detail, imagine the wave in flutter to be circulating around the mouths of both superior and inferior vena cava (Fig. 5). Such a circulating wave may exist in a stable form although a considerable gap exists. It cannot take the short path between the two cavæ, for whenever its crest reaches this muscle bridge, it will find muscle on this cross-route refractory. But supposing that this is the state of affairs, and at a given moment the refractory period of the muscle shortens; the bridge may then be passed and the wave will then circulate, with a much shortened gap, around one or the other cava. The circulation time will decrease and, as a consequence, the refractory period will shorten a little more, tending to secure stability in the new mechanism, even when the original influence which shortens the refractory period is withdrawn. But as the gap is now smaller, conduction will tend to be more irregular and a little slower. In some such fashion it seems probable that the change from stable flutter to a more or less stable fibrillation may be produced.

Support is given to this argument by the change from stable fibrillation to stable flutter under quinidine. Hitherto, the significance of this change seems to have escaped notice. If the quinidine is given to these patients, a state closely resembling what we formerly termed flutter is always brought about, and this has been noted by several workers; but that is not the whole story. Usually the state produced is in reality impure flutter and this disappears invariably when the quinidine is withdrawn and its temporary effects on conduction and refractory period disappear. But in one patient in ten or more, pure flutter becomes established under quinidine; if now no further quinidine is given, the flutter does not disappear, it remains as a stable condition.

In the period of quinidinization, the refractory period is lengthening out and the rate of oscillations is falling. There comes a time when the reaction is at its height and the refractory period is at its longest; it is at this stage that pure flutter appears. We withdraw the quinidine and, as experience tells us, the refractory period recovers after a few (twenty-four to forty-eight) hours. Simultaneously any effect which the drug exerts on conduction must disappear. Thus, although both factors which tended to produce slowing of the oscillations disappear, little acceleration is apparent. A second and new condition of stability is reached. There is here little escape from the conclusion that the circuit contains a longer gap; such a gap must appear as recovery takes place without a corresponding speeding up of the movement. If similar doses of quinidine are repeated on this same patient when the flutter has become quite stable, considerable doses may be given without appreciably affecting the rate of oscillation. There is some slowing, but this is minor in its degree and is to be attributed to the effect of the drug on conduction alone. It is comparable to the slight acceleration which occurs before the flutter becomes stable, a change due to improved conduction following withdrawal of quinidine. The delay of a pronounced fall in rate when the auricle is fluttering is due to the period occupied by closure of the gap by the lengthening refractory period.

Thus, we may conclude that one essential difference between flutter and fibrillation is that the gap is longer in the former.

We now return to the original question; and ask why digitalis converts flutter into the faster-moving fibrillation? Whether the reply is that it must quicken conduction, or whether the reply is that by reducing the refractory period it shortens the path upon which the wave circulates—and the latter is the more promising hypothesis—the explanation of its action will take the same direction; it will be necessary to assume that the quickening is due to a predominant action through the vagus nerve. Just as we explain an increased rate of oscillation in fibrillation itself consequent upon digitalis, so we explain the conversion of flutter in fibrillation; the vagal component of digitalis action will alone induce those changes in the muscle which are theoretically necessary to bring about the quickening which occurs. If you so desire, you may treat the question more upon the lines of direct observation. A material increase of vagal tone quickens the rate of experimental flutter and eventually may force it into fibrillation;[13 15] actually the effect of the direct action of a digitalis body upon flutter has not yet been observed, but we can predict that it would not quicken the movement, for in experiments on dogs, under certain conditions of anesthesia, in which the direct action is alone displayed and the auricles are fibrillating, quickening does not occur; on the contrary, slowing is often seen.

We need therefore have little hesitation in concluding that the conversion of flutter into fibrillation by digitalis is essentially vagal in origin.

**The Influence of Auricular Quickening upon Ventricular Slowing under Digitalis.** As stated, it has generally been assumed that when the auricles are fibrillating, the effects of digitalis upon the ventricle result simply from heart-block. This assumption is not in the strictest sense justified; for it is the rule to find that when the ventricle slows, the auricular mechanism also changes; in greater or lesser degree the movement quickens, and this quickening will exert some influence upon the rate of the ventricular response. Experiments bearing upon this point of view show that at fast rates of beating an increase of rate in the auricle tends in itself to lower the rate of ventricular response; it favors block. The degree in which this influence is responsible for the ventricular slowing cannot be considered in detail on the present occasion. It must suffice if I say that, considering the relatively small change of rate which occurs in the auricle, we do not consider the influence to be a very material one at the rates prevailing.

It is to be noted also that atropine when given in cases of fibrillation produces a fall of auricular rate. This fall of rate will in a small measure favor a rise of ventricular rate, usually attributed entirely to removed vagal tone; the fall of auricular rate is usually small, and is not very materially different in digitalized and undigitalized cases; so that this effect has been neglected in the argument of this article. The magnitude of another factor in the action of atropine is less certain; in experimental fibrillation, if strophanthin is injected and produces a little slowing of the ventricle by a *direct action* rather than by a vagal action, an event which often occurs in dogs under full anesthesia, then a full dose of atropine does not increase the rate of the ventricle but may appreciably *decrease the rate.* If digitalis acted directly upon the muscle in man, and only directly, it seems probable that a similar decrease of ventricular rate with atropine would sometimes be seen in patients; actually this is not the case.

A final word completes what I have to say: It seems to us that the more we explore the facts and view them in the light of the theory of circus movement, as the fundamental cause of flutter and fibrillation, the more clearly is our whole knowledge of flutter and fibrillation illuminated. We cannot believe that the theory would be found to offer a reasonable interpretation of so many and such diverse phenomena unless it were fundamentally true.

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